October 24, 2005

Division of Docket's Management 0607 5 OCT 25 A9:59
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Madam/Sir,

I submit four copies of this petition as a Citizen under 21 CFR 10.30 or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs, requesting that the Commissioner of Food and Drugs recommend scheduling of tramadol under the Controlled Substances Act.

Action Requested

The Petitioner requests that in view of patient safety and public health considerations noted below, the Commissioner of Food and Drugs recommend scheduling of tramadol under the Controlled Substances Act.

Statement of grounds

I submit below the following as foundation for this request and I base my rationale on the "8 factor analysis" described in the CSA as requisite by law in deciding whether to schedule a particular drug.[1]

Controlled Substances Act Excerpt (8 factor analysis)

> *(c) Factors determinative of control or removal from schedules. In making any finding under subsection (a) of this section or under subsection (b) of section 202 [21 USCS Section 812(b)], the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:*
> *(1) Its actual or relative potential for abuse.*
> *(2) Scientific evidence of its pharmacological effect, if known.*
> *(3) The state of current scientific knowledge regarding the drug or other substance.*
> *(4) Its history and current pattern of abuse.*
> *(5) The scope, duration, and significance of abuse.*
> *(6) What, if any, risk there is to the public health.*
> *(7) Its psychic or physiological dependence liability.*
> *(8) Whether the substance is an immediate precursor of a substance already controlled under this title.*

2005P-0430 CP 1

Below each of the eight factors is discussed individually:

(1) Its actual or relative potential for abuse.

- As a clinician, board certified in Internal Medicine and Addiction Medicine, I have seen many cases of tramadol abuse and dependence, (based on DSM IV criteria) over the years since tramadol was introduced (1996). These include cases involving tramadol both as a secondary drug and as the primary, and sole drug of abuse. Tramadol abuse can thus include primary tramadol dependence as well as other forms of substance abuse: 1. Use of tramadol as a secondary drug of abuse, 2. Use of tramadol by patients to attempt to "detox" from other opioids, 3. Substitution of tramadol when the primary substance of abuse is unavailable, and 4. other. The point is that tramadol in these settings has produced tolerance and characteristic withdrawal and has been associated with all the DSM IV criteria for dependence. There is no doubt from empirical observation that tramadol has actual abuse potential.
- Additionally, my colleagues and I have recently published data which documents the relatively high frequency that tramadol was mentioned as a drug of abuse by substance abusing physicians in Alabama and Michigan from 1996 – 2003. Tramadol, overall, was the 3rd most frequently mentioned opioid.[2]

(2) Scientific evidence of its pharmacological effect, if known.

- There is now ample laboratory evidence that tramadol and also particularly its M1 metabolites stimulate mu-opioid receptors associated with euphoria and drug dependence.
- There are now many reports in the literature and in epidemiologic monitoring studies over the years since tramadol's introduction describing more severe abuse liability than previously described.
- There appear to have been misinterpretation and/or misleading information regarding the abuse liability by the manufacturer and/or agents of the manufacturer, including the Independent Steering Committee (funded by the manufacturer), and/or other studies commissioned and funded by the manufacturer.

(3) The state of current scientific knowledge regarding the drug or other substance.

- Tramadol is marketed as a short acting analgesic (Ultram™, Ultracet™, generics) for the treatment of moderate to moderately severe pain. In practice, treatment with Ultram is almost never initiated at at doses greater that 50 mg. Even at that dose, considerable side effects occur.
- According to the manufacturer of Ultram (Ultram Prescribing Information):

  "In a randomized, blinded clinical study with 129 to 132 patients per group, a 10-day titration to a daily ULTRAM® dose of 200

mg (50 mg q.i.d.), attained in 50 mg increments every 3 days, was found to result in fewer discontinuations due to dizziness or vertigo than titration over only 4 days or no titration. In a second study with 54 to 59 patients per group, patients who had nausea or vomiting when titrated over 4 days were randomized to re-initiate ULTRAM therapy using slower titration rates.

A 16-day titration schedule, starting with 25 mg qAM and using additional doses in 25 mg increments every third day to 100 mg/day (25 mg q.i.d.), followed by 50 mg increments in the total daily dose every third day to 200 mg/day (50 mg q.i.d.), resulted in fewer discontinuations due to nausea or vomiting and fewer discontinuations due to any cause than did a 10-day titration schedule.

For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM® can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**"

- In September 2005, FDA approved a sustained or extended release version of tramadol in much higher strengths of 100, 200 and 300 mg to treat moderate to moderately severe chronic pain. Several additional extended release brand name versions of tramadol are expected to file their NDA in the next year.
- Tramadol is a centrally active analgesic which activates the mu-opiate receptors. Opiate receptor binding studies show that tramadol and its primary active M1 metabolite bind to the mu-opiate receptor at clinically meaningful levels. The M1 metabolite is significantly more potent than the parent drug in its mu-opiate receptor binding (Ultram Prescribing Information).
- Studies in a number of animal models of addiction convincingly demonstrate that tramadol has all the hallmarks of a drug with abuse potential: 1) complete or partial substitution for opiates in the opiate dependent animals; 2) suppression or partial suppression of opiate withdrawal signs in animals previously made opiate tolerant.
- In vivo microdialysis measures of dopamine (DA) release within the nucleus accumbens (NAc) shell and the conditioned place preference (CPP) paradigm in rats indicate that tramadol has significant abuse potential (Sprague *et al*, 2002).

- The antinocioceptive effects of tramadol in the rodent model are partially antagonized by the opiate antagonist, naloxone (Raffa *et al.*, 1992). The introduction of opiate antagonists in tramadol dependent rodents and primates precipitates classic signs of opiate withdrawal (Nickel and Aledter, 1987; Wakasa et al., 1994). Administration of high doses of tramadol to rats completely substitutes for morphine (Ren and Zheng, 2000).

(4) Its history and current pattern of abuse.

Background

Scheduling drugs under the controlled substances act is an important process in the prevention and control of substance abuse. Scheduling a drug identifies and designates the drug as having abuse potential. This designation offers protection to the public tantamount to a public "advisory." Likewise, the absence of scheduling is understood by physicians and the public to indicate an absence of abuse potential. The lack of scheduling means the drug will be sampled and prescribed more liberally, and less controlled. In this way then, the lack of scheduling a drug that does in fact have abuse potential serves to send the wrong signal and actually causes increased abuse. The absence of scheduling for a drug with abuse potential could be considered as mislabeling the risk of the drug.

There is a long history in the USA of drugs in the opioid class being initially introduced and not scheduled (pentazocine, propoxyphene, butorphanol, and others) but later found to have significant abuse potential and eventually scheduled. Many lives have been harmed, careers ended, and families damaged when we have not faced the appearance of abuse potential of opioids sooner.

(5) The scope, duration, and significance of abuse.

There are a large number of reports in the medical literature on the abuse of, addiction to and abstinence from tramadol (Barsotti *et al.*, 2003; Brinker A *et a.l*, 2002; Freye and Levy, 2000; Leo *et a.l*, 2000; Liu *et al.*, 1999; Ripamonti *et al.*, 2004; Scherbaum *et al.*, 2005; Soyka *et al.*, 2004; Thomas and Suresh, 2000; Yates *et al.*, 2001).

According to DEA (http://www.deadiversion.usdoj.gov/drugs_concern/tramadol.htm):

> "Poison Control data (2002 AAPCC Annual Report) indicates that there were 2,400 exposures of tramadol reported to poison control centers. Of those, 108 resulted in a major medical outcome and 8 resulted in death."

The DEA further notes that:

> **"Illicit Uses:**

Tramadol is abused for its opiate effects. The Drug Abuse Warning Network (DAWN) is a database which provides data on drug related episodes reported by hospital emergency rooms. In 2002, there were 1,714 episodes for tramadol and a total of 7,890 episodes from 1998 through 2002. DAWN medical examiners reported that tramadol was involved in 95 drug-related deaths in 2002 and a total of 382 deaths from 1998 through 2002.

The National Forensic Laboratory System (NFLIS) and System to Retrieve Drug Evidence (STRIDE) are both DEA databases that collect scientifically verified data on analyzed samples in state/local and DEA forensic laboratories, respectively. In 2003, there were 267 exhibits of tramadol in NFLIS and 2 exhibits in STRIDE. These relatively small numbers are most probably a reflection of the uncontrolled status of tramadol in the U.S.

User Population:

The current pattern of tramadol abuse in the US involves street drug addicts, chronic pain patients, and health professionals. The lack of control and lack of urine toxicology screen for this medication have probably contributed significantly to the availability of this drug.

Illicit distribution:

Like other legal pharmaceuticals with abuse potential, diversion of this medication occurs in a number of ways including prescription fraud. As an uncontrolled substance, there are no CSA regulations regarding manufacturing, distribution, or prescription of this medication."

- According to the National Survey on Drug Use and Health (2002), approximately one million persons have consumed Ultram for non-medical use. Significantly, this is approximately half the incidence of non-medical use for OxyContin™ and approximately the same incidence reported for the non-medical use of Dilaudid™.

(6) What, if any, risk there is to the public health.

- Increased risk of tramadol abuse and overdose that will be experienced once tramadol is released in the higher dosage extended release form (as was seen with introduction of Oxycontin).

(7) Its psychic or physiological dependence liability.

Tramadol Abuse and Dependence

There is currently no question that Tramadol has potential for abuse and addiction. Many cases of abuse and dependence (i.e. addiction) to tramadol have been reported over the years since it was released. (Senay EC, et al 2003, Ripamonti, et al 2004, Skipper GE, et al 2004, Soyka et al 2004). Tramadol abuse has been reported both as a primary drug of abuse, and also where it is has been used in substitution for other addictive drugs. In other words, people that have had no history of any substance abuse or addiction have taken Tramadol and become addicted to it. Tramadol addicts report typical addiction syndromes including heavy use, using up to 50 or more pills per day, faking prescriptions, seeking multiple doctors to prescribe it, Tramadol thefts, attempt to quit taking it, Tramadol seizures, etc.. Contrary to evidence presented to the FDA Drug Abuse Advisory Committee by the manufacturer in the 1990's, tramadol can be substituted and used to detoxify patients from other opioid addictions. (Sobey PW, *et al.,* 2003, Tamaskar R, *et al.*, 2003). Tramadol withdrawal syndrome has been reported to be severe. (Barsotti, 2003) Individuals addicted to other drugs have reported substituting tramadol because it is more readily available.

There have been nearly a thousand spontaneous reports to the FDA's MedWatch system regarding tramadol abuse, tramadol dependence, and withdrawal syndrome following abrupt abstinence from tramadol. There have been a reports of tramadol abuse and dependence associated with grand mal seizures. (Yates *et al.*, 2001).

Among individual opioids listed in the 2001 and 2002 annual reports of the American Association of Poison Control Centers Toxic Exposure Surveillance System, tramadol ranked second to oxycodone in number of exposure cases (Watson et al 2002). In the Drug Abuse Warning Network (DAWN) report in 1999 there were 1113 estimated emergency room episodes involving tramadol as compared to 1313 for hydromorphone and 512 for meperidine.

At the Cincinnati Drug and Poison Information Center tramadol was studied and they report there were 362, 107, 515, and 326 calls related to tramadol abuse calls in 1995, 1996, 1997, and 1998, respectively. (Krummen *et al.*, 1999). Furthermore the Cincinnati police documented diversion of 7,258 doses of tramadol from 9/97 –12/97 and 11,385 doses in 1998. Tramadol was listed in the top 10 most diverted prescription drugs in Cincinnati at that time. Their conclusion was that physicians need to consider the abuse potential and monitor patients for dependence and that tighter controls should be considered.

There has been a significant incidence of tramadol abuse by health professionals. We recently published a report of combined data from the Michigan and Alabama Physician Health Programs involving 859 health professionals since 1996 and we found that tramadol was the third most frequently mentioned opioid by substance abusing physicians. (Skipper et al, 2004)

Despite reports from monitoring agencies and case reports that suggest tramadol has a significant risk of abuse, the manufacturer has sponsored research reportedly showing a low risk for abuse. Conclusions from these studies are problematic, however, due to errors in selecting numerators and denominators. In one study the total number of individuals worldwide who had taken tramadol was divided by the limited number of cases of abuse detected through a "key informant" network. Dividing the larger number of everyone who had taken tramadol by only a fraction of cases of known abuse leads to a far reduced estimate of abuse liability. (Cicero et al, 1999) Another example of this phenomenon is in the report by Knisely and coworkers (Knisely et al, 2002) where the total number of physicians admitting abuse of tramadol was divided by the total number of physicians being monitored, without measuring the percent of these physicians actually taking the drug. In fact in their report, the majority of participants in the population studied were not known to have ingested tramadol and likely were not exposed to the drug. Since 140 participants were known to have ingested tramadol and 15 of these were judged to be abusing tramadol, the actual abuse/dependence liability of tramadol was 10.7% not 0.69% as they erroneously concluded. Obviously if a drug is not taken it can have no abuse liability.

In April 1998 the FDA cited the lack of comparative data as a major reason for the committee's decision to not recommend scheduling tramadol.[3] Before generic versions of Tramadol were introduced, the branded version was heavily detailed and marketed to physicians' offices and currently it is in the top 30 most prescribed drugs in the US.[4] Early in tramadol's post-marketing course, there were reports of reinitiation of abuse, cases suggestive of neonatal withdrawal, and cases of withdrawal and dependence. These reports were sufficient to result in the issuance of a Dear Health Care Professional letter and the addition of strong warnings and precautions to the labeling. The DAAC met in 1998 and reviewed findings including numerous reports of typical dependence syndromes with the use of tramadol either as a single agent or in combination with other addictive drugs[5] (FDA/DAAC, 1998). Post-marketing surveillance ~~as~~ reported by the ISC (Cicero *et al.*, 1999) suggests a low rate of abuse and dependence (1-2 per 100,000 patients). (Cicero *et al.*, 1999). It should be noted that the ISC has obtained case reports from "key informants" and likely are detecting only a fraction of the many cases of tramadol abuse or dependence. The FDA has continued its position and has not recommended that tramadol be scheduled. Recently, the DAAC was dissolved as a distinct advisory committee of the FDA.

Many who work with impaired health professionals have observed continuing problems with tramadol abuse and dependence. Tramadol has been heavily marketed to physicians, and samples have been readily available. Minimal or absent abuse potential is mentioned frequently by drug company salespersons, according to physicians interviewed in the Alabama program. Thus, availability and false reassurance regarding risks may be factors that have increased inappropriate use.

Awareness by many physicians in recovery that tramadol is not usually measured in typical random urine drug screens may also have increased the risk of relapse on this drug.

In conclusion, inadequate attention has been given to identifying tramadol abuse and dependence, particularly among health professionals who may be at particular risk. The presence of abuse warnings in the label alone, without scheduling under the CSA, is inadequate to prevent tramadol abuse among physicians at an incidence greater than six controlled opioid drugs that are controlled.

Historically, there has been a recurring tendency to release opiate analgesics which are initially thought to have little or no addiction potential but are later identified as addictive and require scheduling. Any opiate that stimulates mu receptors, either directly or via active metabolites (including tramadol), should be assumed to have addictive potential. In summary, both the experimental and clinical literature indicate that tramadol has significant abuse potential, consistent with its pharmacology. This abuse has significant public health policy implications. Lessons learned from Oxycontin indicate that the sustained release formulations of tramadol may carry additional safety and public health consequences. All available data would support the scheduling of tramadol at the level of Schedule III.

Environmental Impact

According to 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

Economic Impact Statement

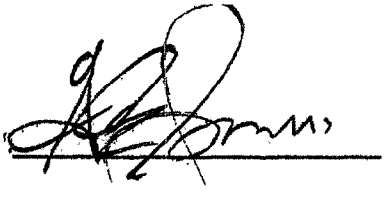
According to 21 C.F.R. § 10.30(b), petitioner will, upon request by the Commissioner, submit economic impact information.

Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Notices regarding this petition should be addressed to: Gregory E. Skipper, MD, 19 S. Jackson Street, Montgomery, AL 36104, Tel: 334 954-2596.

Respectfully,



Gregory E. Skipper, MD
Fellow, American Society of Addiction Medicine

References

Barsotti CE, Mycyk MB, Reyes J. Withdrawal syndrome from tramadol hydrochloride. Am J Emerg Med. 2003 Jan;21(1):87-8.

Brinker A, Bonnel RA and Beitz J: Abuse, dependence, or withdrawal associated with tramadol {letter}. Am J Psychiatry 2002; 159:881.

Cicero TJ, Adams EH, Geller A, Inciardi JA, Muñoz A, Schnoll SH, Senay EC, Woody GE: A postmarketing surveillance program to monitor Ultram® (tramadol hydrochloride) abuse in the United States. Drug Alcohol Depend 1999; 57:7-22.

FDA/DAAC: Food and Drug Administration Center for Drug Evaluation and Research Drug Abuse Advisory Committee, April 28, 1998 {transcript}. Washington, DC: Associated Reporters of Washington, 1998.

Freye E, Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): A case study. European Journal of Pain 2000;4:307-311.

Knisely JS, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. Drug Alcohol Depend 2002; 68:15-22.

Krummen K, Nelson E, Tsipis G, Siegel E and Bottei E. Cincinnati Drug and Poison Information Center, Children's Hospital Medical Center, Cincinnati, OH.

Leo RJ, Narendran R, DeGuiseppe B. Methadone detoxification of tramadol dependence. J Substance Abuse Treatment 2000;19:297-99.

Liu ZM, Zhou WH, Lian Z, Mu Y, Ren ZH, Cao JQ, Cai ZJ. Drug dependence and abuse potential of tramadol. Zhongguo Yao Li Xue Bao 1999;20:52-4.

Nickel B and Aledter A. Comparative physical dependence studies in rats with flupirtine and opiate receptor stimulating analgesics. Postgraduate Med J 1987;63:41-43.

Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. JPET 1992;260(1):275-85.

Ren Y-H, Zheng J-W. Influence of tramadol on morphine discriminative behaviour in rats. Acta Pharmacol Sin 2000;21(10):924-926.

Ripamonti C, Fagnoni E, De Conno F. Withdrawal syndrome after delayed tramadol intake. Am J Psychiatry. 2004 Dec;161(12):2326-7.

Scherbaum N, Kluwig J, Meiering C, Gastpar M. Use of illegally acquired medical opioids by opiate-dependent patients in detoxification treatment. Eur Addict Res. 2005;11:193-6.

Skipper GE, Fletcher C, Rocha-Judd R, Brase D. Tramadol abuse and dependence among physicians. JAMA. 2004 Oct 20;292(15):1818-9.

Sobey PW, Parran TV Jr, Grey SF, Adelman CL, Yu J. The use of tramadol for acute heroin withdrawal: a comparison to clonidine. J Addict Dis. 2003;22(4):13-25.

Soyka M, Backmund M, Hasemann S. Tramadol use and dependence in chronic noncancer pain patients. Pharmacopsychiatry. 2004 Jul;37(4):191-2.

Sprague JE, Leifheit M, Selken J, Milks MM, Kinder DH and Nichols DE: In vivo microdialysis and conditioned place preference studies in rats are consistent with abuse potential of tramadol. Synapse 2002; 43:118-121.

Tamaskar R, Parran TV Jr, Heggi A, Brateanu A, Rabb M, Yu J. Tramadol versus buprenorphine for the treatment of opiate withdrawal: a retrospective cohort control study. J Addict Dis. 2003;22(4):5-12.

Thomas AN, Suresh M. Opiate withdrawal after tramadol and patient-controlled analgesia. Anaesthesia 2000;55:826-27.

Ultram prescribing information (2005). Physicians' desk reference, Thomson PDR, Montvale, NJ 07645.

Wakasa Y, Kawaguchi T, Yanagita T. Withdrawal characteristics following frequent intravenous administration of several opioids in rats. Japan J Alcohol & Drug Dependence 1994;29(1):40-51.

Watson WA, Litovitz TL, Rodgers GC Jr, *et al.* 2002 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med. 2003; 21:353-421.

Yates WR, Nguyen MH and Warnock JK: Tramadol dependence with no history of substance abuse {Letter}. Am J Psychiatry 2001;158:964.

---

[1] *Controlled Substances Act Excerpt (8 factor analysis)*

(c) Factors determinative of control or removal from schedules. In making any finding under subsection (a) of this section or under subsection (b) of section 202 [21 USCS Section 812(b)], the Attorney General shall consider the following factors with respect to each drug or other substance proposed to be controlled or removed from the schedules:

(1) Its actual or relative potential for abuse.

(2) Scientific evidence of its pharmacological effect, if known.

(3) The state of current scientific knowledge regarding the drug or other substance.

(4) Its history and current pattern of abuse.

(5) The scope, duration, and significance of abuse.

(6) What, if any, risk there is to the public health.

(7) Its psychic or physiological dependence liability.

(8) Whether the substance is an immediate precursor of a substance already controlled under this title.

[2] Skipper GE, Fletcher C, Rocha-Judd R, Brase D. Tramadol Abuse and Dependence Among Physicians. JAMA. 2004;292:1818-1819

[3] Food and Drug Administration Center for Drug Evaluation and Research Drug Abuse Advisory Committee, April 28, 1998 {Transcript}. Washington, DC, Associated

Reporters of Washington, 1998, 225 pp. Available on the Internet at: www.fda.gov/ohrms/dockets/ac/98/transcpt/3411t2.rtf Accessed 8/18/04

[4] www.RxList.com

[5] Ehrenreich H and Poser W: Dependence on tramadol. Clinical Investigator 1993; 72:76.